UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

MUTUAL RECOGNITION AGREEMENT (MRA)

PUBLIC MEETING

Rockville, Maryland

Wednesday, December 8, 1999

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AGENDA: PAGE

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P R O C E E D I N G S

(9:04 a.m.)

OPENING AND WELCOME

MR. GAYLORD: I'd like to give a warm welcome to each of you. My name is Charles Gaylord from the Office of International Programs. On behalf of the Food and Drug Administration I would like to welcome you to today's public meeting. I know some of you have come from a long distance, and some from near. But no matter the distance, we're here to discuss a very important topic.

The meeting today will look at the action that has been taken to implement the Sectoral Annex for Pharmaceutical Good Manufacturing Practices (GMP) to the Agreement on Mutual Recognition (MRA) between the United States and the European Community.

When the Mutual Recognition Agreement was signed last year, it was a significant milestone that was the

culmination of years of hard work by many people both within the EU and the FDA. It was timely when it was signed for several reasons.

First, a rapidly changing and increasingly global marketplace regarding the products FDA regulates. Secondly, there was a need to maximize FDA's resources. Third, there was the enactment of the Food and Drug Modernization Act of 1997, which incorporates into the FDA's mission the concept of developing agreements with other countries.

The Modernization Act provided a framework for the MRA, and its sweeping provisions endorse many of the things FDA was already doing to keep up with its expanding obligations of protecting the public health.

The stated purpose of the Pharmaceutical Annex is to, and I quote, "govern the exchange and normal endorsement of official good manufacturing practices inspection reports after a transition period

aimed at determination of the equivalence of the regulatory systems of the Parties."

So, as this process unfolds, during this transition period, we have a three year window to accomplish many things. Now, the Agreement became effective on December 7th of 1998.

During this transition period, the FDA is participating with its EC member states and the regulatory authorities there, a number of assessment activities with its counterparts, to look at pharmaceutical GMP practices.

It includes such things as the conduct of joint training, and the exchange of legal and regulatory information.

These activities will enable FDA to assess the equivalence of its counterpart authorities in the EC, and conversely will allow these authorities to assess the equivalence of FDA. Today, as you will note in your agenda, in your packet, presenters

will discuss the following items.

After the introductory remarks, we'll have an overview of the Pharmaceutical GMP Annex. Secondly, there'll be highlights of the first Joint Sectoral Meeting that was held May 18th and 19th of this year. Then we'll look at equivalence assessment, the development of an alert system, and public transparency of MRA processes.

Now, before we get started, I'd like to make a few announcements. In terms of the structure of the meeting itself, after the presentations are given, there'll be a fifteen minute break, followed by presentations from the audience. So, three people from the audience have stated that they would like to give presentations, so we've allotted time for that.

After that, there will be two panels convened to answer any questions that you might have. Now, you can ask your questions by way of index cards that will be

in your packets.

They can be passed to the aisles to you, to your right and left, so that they can be collected and passed to me. Or you can use the floor mikes on either side of the room, and ask the questions directly to the panelists.

The questions on the index cards will be read as time allows. We've allowed members of both panels to respond. Now, since the meeting is being transcribed, I would ask that each of you give your name and organizational affiliation, whether you're using the index cards, or asking the questions directly.

Now, in terms of housekeeping items. The layout of this building compared to Parklawn is comparatively simple. Right outside the door we have the restrooms immediately across the hall. There is a pay phone that is near the guard's desk to the right of this room.

There is also a phone here in the room to my left, and you can dial nine to reach the outside. We have provided coffee and tea for your refreshment. There is a vending room to my left outside of these doors for additional items.

Now, to give us our introductory remarks, we have Ms. Holston from the Office of International Consituent Relations. She is the Deputy Commissioner of that office.

In that capacity, Ms. Holston provides executive level policy and program direction for FDA’s interactions, information exchanges, and liaison activities with a variety of domestic and international external audiences.

Ms. Holston is the acting director of FDA Office of International Programs, and as the Deputy Commissioner for International Constituent Relations, her principle goal is threefold.

One, is to enhance FDA’s working

relationships with external organizations. Two, to increase understanding of the agency's operations and objectives.

Three, to encourage appropriate collaborations on vital public health issues. She plays a key executive role in directing FDA's relationships with numerous foreign governments and international organizations. It is my pleasure to present Sharon Holston. Sharon?

STATEMENT OF MS. HOLSTON

MS. HOLSTON: Good morning, and thank you, Charles. First of all, I also want to welcome all of you to this third public meeting on the Mutual Recognition Agreement. We're going to focus on the Pharmaceutical Annex to that agreement.

About three years ago when we held one of these public meetings some of you may have been here. But whether you were or not, my title at that time was Deputy Commissioner for External Affairs. I think the fact that

it's now International and Constituent Relations is an acknowledgement on the part of FDA that international programs is playing an increasingly more important, more dominant role, in everything we do to protect the public health.

So, this meeting on the Mutual Recognition Agreement is also part and parcel of FDA moving aggressively and forcefully onto the global scene.

The MRA which is the topic today represents really a quantum leap in that process. That's why we want to share with you the developments that have taken place so far to outline some of our plans, and to invite your comments on issues that are related to the implementation of the Agreement which began exactly one year and one day ago.

Why is this MRA so significant? Because after the three year implementation period, it should enable FDA to rely on our

counterparts in the European Union to inspect facilities in their countries that manufacture drugs for the United States market.

Although FDA will continue to have the final responsibility for the compliance of the imported regulated products, making certain that they do, in fact, comply with US standards, this large scale reliance on foreign regulatory information that is critical for the assurance of the quality of the products that are being exported, this reliance on foreign data is really unprecedented in our history as far as meeting our public health protection mandate.

I have to say that it is not a move that we have taken lightly, or without adequate protections. But we did go ahead and do this, after much, much discussion within the Agency, for several very persuasive reasons. Charles mentioned one of them, of course, and that is the FDA

Modernization Act of 1997, which in fact absolutely requires the Agency to advance the development of MRA's with the European Union for almost all of the products that we regulate.

But the Modernization Act really acknowledged the logic of some developments that have been under way for many years, and have sort of gotten or risen to a climax in the last several years.

One of these factors is the ever widening gap between FDA's inspection workload, and the resources that we have to carry it out. Since the start of this decade, imports of FDA regulated products have grown from about one and a half million line entries per year to five and a half million line entries in 1999. That's a 360 percent increase.

Because we literally haven't had the resources to hire more people to do the job, the number of FDA employees who are

actually surveying these imports has remained just about constant, at around 770, or so.

In the same decade, our inspectional responsibilities have gone up about thirty-two percent, from about 87,000 business establishments to about 115,000 business establishments. Most of these are facilities that are using methods and equipment that are a lot more sophisticated, a lot more complex, and therefore more difficult to inspect than was the case a decade ago.

Yet, during that same ten year period, we could only increase the number of FDA inspectors by something less than ten percent. So we went from about a thousand to just under 1,100.

So just these two factors alone are two of the indicators of what we have to acknowledge are some relentlessly mounting pressures on the Agency. If you'll bear with me, I have just a few more examples.

In the last decade, sales of dietary supplements have increased from about $3 billion a year to $20 billion a year. Adverse event reports involving human drugs have gone up from 75,000 to 230,000 a year. Bio- medical research expenditures that fuel the development of hundreds of new highly complex regulated products have tripled to $20 billion.

The sales of human drugs, medical devices, and animal drugs between 1993 and this year have gone up somewhere between seventy percent and about eighty-five percent.

So you can see that during the last decade, there's been really a prodigious enlargement of our workload.

The resources have been relatively stagnant over that same period of time. In constant dollars, the budget has gone up from $809 million in 1993 to $915 million in the current fiscal year. But more than a

third of that is committed to four specific programs.

That's drug reviews, food safety, enforcement of the tobacco rules, and surveillance of mammography facilities.

So as a result, the number of employees who handle all of the FDA programs except for drug reviews has actually declined since 1992. This is something that we're seeing across the board.

So, we need help. One way of getting it is by utilizing GMP inspectional information that's provided to us by, and this is very important, equivalent regulatory counterparts in the European Union. In return, performing GMP inspections that they need done in this country.

When I meet with and speak with my counterparts in Europe, believe me, we're not the only ones that are facing this kind of situation, where the workload is far outstripping the resources that we have to

handle it. So we both see significant advantages in having agreements of this sort.

But even with all of that, and I know I've given you a lot of numbers about, you know, workload, and resources, and people, and things like that, even with all of that, the legal requirement from FDAMA, the budgetary factors, these are not the only, or even the most important forces that are really driving FDA into partnership with our colleagues in Europe.

We're not moving in this direction because we can't afford to do anything else. Far from it. I think the international links that we're forging, and sometimes they feel very unsettling. It feels, you know, umm, we're not really sure if this is something that we should be, you know, sort of running toward.

But these links are really an outgrowth of an historical process that I think in the long run is far more compelling

than anything that has to do with the budget figures. It's a process for which I think we have to be really grateful.

In fact, I'm confident that even if we had all the resources we need, we would still be responding to the growing awareness that public health as a responsibility is an indivisible responsibility.

That by reaching out beyond our borders, working with others to raise standards, that we can collectively more effectively accomplish our goals.

Certainly more efficiently than we could ever do if we tried to do everything by ourselves. I think this MRA is just an indicator that the Agency is acknowledging the critical role we play as a member of, you know, what is commonly being referred to as the global public health community.

We have a major role to play in that community, not only in helping our counterparts with protecting the health of

their citizens, but having them help us with the protection of the public health of our citizens. So, we are very grateful that you are here with us today to learn more about the MRA. We thank you for joining us.

I had intended to be here for the entire session this morning. But there is an international issue that is forcing me to go back across the street, and talk to some of my buddies in the State Department. So, I'm going to have to run.

But again, I hope that you find this session this morning very helpful and informative. We look forward to having a continuing dialogue with you this MRA, and others that undoubtedly will happen in the future. So thank you again.

MR. GAYLORD: Sharon, thank you for those introductory remarks. Our next speaker is Joseph Famulare, who is the director of the Division of Manufacturing and Product Quality, and the Center for Drug Evaluation

and Research. He is the head of the Project Management Team responsible for helping to implement the MRA.

He is also the co-chair of the Joint Sectoral Committee. He will give an overview of the MRA's pharmaceutical GMP annex by describing the framework for achieving mutual recognition of GMP inspections. Joseph?

STATEMENT OF MR. FAMULARE

MR. FAMULARE: Thank you, Charles. It's a pleasure to be here this morning to share our progress to date on implementing the Mutual Recognition Agreement. Today marks one year and one day since the actual agreement has entered into force, in terms of the United States, as it was published final in the Federal Register, December 7th of 1998.

So I would like to give an overview of the Mutual Recognition Agreement. With the help of the members of my team here

today, go over the progress we've made in the various areas.

(Pause)

MR. FAMULARE: Pardon me? Arrow key. Okay, there we go. Technologically in lined; as Sharon mentioned, there's much changing technology that FDA is having to deal with, as you can see right here every day.

First of all, I'd like to give a little bit of a background and history on the Agreement itself. Initial discussions of a Mutual Recognition Agreement really began in 1989 as to the practicality of entering into such an Agreement. In actuality, in April of 1994, the actual discussions began, the actual negotiation process.

You could see, it took several years of really detailed, and many negotiations, and many issues to be settled in terms of the overall Mutual Recognition Agreement, and particularly with the

Pharmaceutical Annex that we're discussing today.

Until a tentative Agreement was initialled on June 20th of 1997, and then of course, finally signed by President Clinton over in the UK on May 18th 1998. As I mentioned at the start of my talk, there was then a procedure in order to enter this Agreement into force on both the U. S. side, and the European side.

From our standpoint, because of the nature of this agreement, and the fact that it was binding, it was felt by FDA that we needed to go to a rule making process in order to enter into force with this Agreement.

Therefore, during 1998, we published a proposed rule, took in comments, then on, as I said in the beginning of my talk, we published this Agreement, in terms of the FDA actually, both the Pharmaceutical and the Medical Device Annex on December 7th

of 1998 under 21 CFR Part XXVI which actually entered the Agreement into force. This actually for the US marks the beginning, the first year of the three year transition period.

What does mutual recognition actually mean? It means accepting the other party's conformity assessment procedures. This is not a harmonization process, and I'll bring that up again. Sharon already emphasized how this is about equivalence.

This is a concept which was established by the World Trade Organization, as Sharon very well went through in her introductory remarks, there are realities as to why we got into this Mutual Recognition Agreement, particularly in terms of diminishing inspection resources, and our need to really cover the pharmaceutical industry and, in the case of medical devices, a need to cover the industry globally, as we're in a global economy.

So therefore, this overall Mutual Recognition Agreement came into effect in force with specific Sectoral Annexes. Some of those Annexes, just to make folks aware, you know are things really not related to food and drug, such as recreational craft, electrical communications, and so forth.

I guess maybe it'd be more interesting to be the co-chair on the recreational craft. But unfortunately it's not under the purview of the Food and Drug Administration. But those are some of the many product areas that are part of this overall umbrella of Mutual Recognition Agreement.

Focusing again on the Pharmaceutical Annex, one of the main features is that it emphasizes our finding equivalence with the fifteen member states. Each one of those member states will be dealt with individually in terms of recognizing their equivalence.

The important part of this Agreement is, really I guess the ultimate goal, is that it will lead to the exchange and endorsement of inspection reports.

Once we go through this equivalency assessment process, we will be able to receive an inspection report from our European counterparts that we have found equivalent, and be able to normally endorse, to quote the Agreement itself, that inspection report, to use it as if it were our own report. But again, as Sharon pointed out in her introductory remarks, the actual compliance decision will be up to the FDA.

Again emphasizing strongly that this Agreement is really based on the equivalence of regulatory systems. Meaning that the regulatory system in the authority that we're evaluating should be able to provide the same level of public health protection as our own system, of GMP's and regulatory enforcement, the overall system.

Not that they be the same as a harmonization situation might be, but equivalent.

This Annex of the Agreement, the Pharmaceutical Annex, is managed by a Joint Sectoral Committee, with representatives from both the EC and the European Union -- I'm sorry, and the US side, FDA side. I am the co-chair for the United States FDA.

My counterpart, my colleague in the European Community is Steve Fairchild, who acts as a coordinator from the European Medicines Evaluation Agency, under the auspices, of course, from the European Commission itself, under Emma Cook, in Director General Three.

I won't get into all the details of how the European Commission works at this juncture. But I'll just tell you that from their side, you have Steve Fairchild coordinating with the European's Medicine Evaluation Agency, and representatives from various member states on the Committee from

the European Commission side.

From our side, of course, the Joint Sectoral Committee consists of what we call our Project Management Team, the Representatives from each center that will make up, and ORA, that will make up the members of this team, which include myself, Brian Hasselbalch from CDER, Ray Mars from ORA, Judy Gushee from CVM, and Merton Smith from the Office of International Affairs.

So, all these various factors are working together within the Agency to be part of this committee, internally, the Project Management Team. They in turn report to senior managers at the Commissioner's level, ORA, and all the Center levels, which comprises the Steering Committee internally.

As I said, one of the main features of this Annex was in terms of the Agreement was reached that we would have a transition period of three years in order to do this important equivalency determination.

As I've said, we're one year into that now, where we will assess the equivalence of each of the regulatory authorities, and the overall European Commission itself, which has set the directives and guidelines for each member state in this area.

Other tasks that we're put upon to do within this transition period is to determine what essential information belongs in this inspection report and format, because this is the key document that's going to be exchanged between member states and the FDA.

We're also going to develop a two way alert system during this period. You'll hear more details on the progress of these things from the various Project Management Team members as they come up.

Then at the end of this three year transition period, there will be a determination of equivalence by the Joint Sectoral Committee. There will be one vote

from each side, from both the US and the EC side, to determine whether a particular authority is equivalence.

These will only be positive determinations. If, in other words, if both sides agree that an authority is equivalent, that authority will be listed as equivalent. If another authority isn't there yet, that vote may agree upon that, but there won't be anything published or put forward about that. It still remains to see that that authority may be found equivalent.

Again going over the basics of the Annex itself, you can see what products are covered. Basically it's human, animal drugs, vaccines, therapeutic biologics, and active pharmaceutical ingredients. The main exceptions here would be obviously human blood and plasma products, veterinary biologicals, tissues and organs, medical gases, radio pharmaceuticals, investigational new drugs, and biological in-vitro diagnostic

devices.

This is to remind everybody of the member states that are part of the European Union, these are the authorities that are on the table for being evaluated in the European Union. You could also keep in the back of your mind that, of course, the European Union has plans in the future to extend to other authorities. But for now, this is who we are dealing with.

Just to focus on the inspection report format, we would expect to have reports in an agreed upon format between both the EC member states, and the US FDA where each authority can normally endorse, except the conclusions from these inspection reports. Of course, as Sharon said earlier, there are protections built into the process.

Those exceptions, in terms of inspection reports, of course would be if we found material inconsistencies in the report, inadequacies, quality defects, for example,

in products that were identified in post market surveillance, or specific evidence of concern on consumer safety.

So, if there is any level of concern to the public health, product defects, or the reports themselves are inadequate, there are recourses within the Annex of actions that could be taken. Up to, you know, which includes up to going out and having, for example, the authority, let's say the FDA go and do the inspection themselves, to satisfy themselves that product being imported is of acceptable quality.

Another important feature of the Pharmaceutical Annex is that there is to be an exchange of information, a type of a collaboration effort between both the European Commission and the US FDA. For example, when there are proposals to introduce new controls, or to change regulations or inspection procedures, we will collaborate with each other in doing these.

There'll be an added step in collaborating on new GMP's regulations. Because it would certainly have an effect on the equivalence that, let's say, would have been established. It will also serve, again, to have more input from both US and EU side on these guidance or regulation documents as they develop.

Article Nineteen of the Annex speaks about the exchange of quality information, information that each other has on product reports, or corrective actions, such as from our standpoint, drug product defect reports, the sharing of recall information, information about import consignments that have been rejected, and any regulatory and enforcement problems.

So there'll be, for example as now, each authority may look at this to see if there's an overall industry problem. As industry is global, well now, we'll start looking at this, at industry problems

globally with our European counterparts. So this is an important feature in the Annex.

Then of course, there will be a two way rapid alert system, as part of the Agreement under Article Twenty, which will call for early alerts when information becomes known that necessitates additional controls or product removal.

Some of the implications of this Annex that we need to think of as we go through this meeting today are that we're into this Agreement to make more efficient and targeted use of diminishing inspection resources.

By having regulatory authorities collaborating, as I said in my earlier slide, we might expect faster action against adulterated products. Especially, you know, as we deal in an international arena now.

As we collaborate this could, you know, have a dual effect of maybe being a supporter or barrier for regulatory change.

When I say support for regulatory change, you will have the collaboration of all of the international community as we go through these changes.

The reason I use the term barrier is that as you bring more parties to the table, it may become more complicated to bring these changes into effect.

As each side looks at each other, the equivalence assessment process may actually result in improvements, as we put ourselves under the microscope, as the US is going to be evaluated by our colleagues in the EU, and as we evaluate our European colleagues.

This is to give you a high level view of our overall implementation plan. Early in the process of the transition period, we began the development of the two way rapid alert system. Focusing right now on recalls. We started that, as I say, in February of 1999. We're continuing to

develop that with our European counterparts.

We're now engaging in the process of working -- in the early stages of working on what will be a common report format. What would satisfy both authorities in terms of the exchange of an EIR. That process is ongoing now.

Of course, we've begun the actual equivalency assessment process, which includes not only joint inspections, which will come up in more detail in later presentations, and is always of interest to industry. When will those happen, and how will those be?

But remember, this is the overall evaluation of each authority's regulatory system. Do you have enough investigators? Are they trained? Do you have enforcement follow-up, in addition to the actual on- site inspections?

Of course, the big beginning part of this process is to actually look at the

laws and regulations from each member state, and for the EU to look at our laws and regulations. You'll get more detail about how that process is going in our next presentation.

Remember that the transition period ends in December of 2001, at which time there should be a, as I say, a meeting of the Joint Sectoral Committee to decide what authorities are found equivalent. Then for those authorities found equivalent, and as part of the equivalency assessment process, it's not only authorities, but it's also process. For example, solid oral dosage form sterile drugs.

Those authorities and processes within authorities that are found equivalent, for example, by FDA, will be declared in a Federal Register announcement. Then we could, beginning and entering into the operational phase with those particular authorities.

Just one overall remark on the implementation plan. This is a plan. It depends, like any other plan, on factors beyond our control as we enter into it. One of those being our ability to have resources to implement the plan against all other work that FDA has. Second, our ability to interact with our European authorities in order to implement the plan in terms of their needs, resources, and so forth, to do this.

With that, I'll conclude these brief remarks and the beginning part of our session to go on to our other folks. Of course, there'll be the opportunity to ask questions later on in the session. Thank you very much.

MR. GAYLORD: Joseph, we'd like to thank you for that overview of the Pharmaceutical GMP Annex. One of the things that Joseph mentioned was the Joint Sectoral Committee.

Our next speaker, Raymond Mars, is

the Special Assistant to the Director of Division of Emergency and Investigational Operations, and the Office of Regulatory Affairs. He's going to report on the first Joint Sectoral Committee meeting that was held last May 18th and 19th of this year. So, Ray?

STATEMENT OF MR. MARS

MR. MARS: Good morning, everybody. Why did you turn the lights out when I came up here? I did shave this morning. No, they're fine.

Anyway, as Charles said, we had the first meeting with the Europeans May 18th and 19th. It was here in Rockville, right next door at the Parklawn Building. There were twelve representatives present from the EU, and I'll just go through some of the basics of the meeting with you so you had some understanding of what we were doing.

There were two people there from the Directorate General Three. I think that

name is being changed right now. They're undergoing some reorganization process. But that is the group within the EU governmental bureaucratic structure that's overseeing the implementation of the MRA.

There were two people from the EMEA, European Agency for the Evaluation of Medical Products. As Joseph said, that is our counterpart group to the Project Management Team that is helping to organize implementation of the MRA for the Europeans.

There are also representatives there from Denmark, France, Germany, Ireland, and the UK. Some countries were obviously not there, since there are fifteen member states in the EU.

FDA had twelve participants, so we outnumbered them. We felt good. There were about six or so additional presenters besides the twelve participants. We had three representatives from the Center for Drugs, two representatives from the Center for

Biologics, two from Office of International and Constituent Relations. They just changed the name. I have trouble catching up. It used to be Office of International Affairs.

One representative each from Center for Veterinary Medicine, and ORA. Three representatives from our Chief Counsel's Office. Chief Counsel weighed in heavily, as you can see, as they sometimes tend to do.

Three centers were represented because, as Joseph said, the MRA covers pharmaceuticals that are human, veterinary, as well as biological. So that was the make-up of the meeting generally.

We had an agenda. These are some of the topic items that were on the agenda in terms of reference, which I'm going to discuss in some detail here in a minute. We talked about communication. There was a discussion about confidentiality, which was a big issue. A two-way alert system, which deals with the recalls, and sharing emergency

information that Sylvia Henry is going to talk to you about in a few minute.

Working programs, the equivalence assessment program, and Brian Hasselbalch is going to talk to you about that. That's the approach that we were going to take, as well as they were going to take, to conduct this equivalence assessment. Then we came up with some action items. So it was a good meeting. We had an agenda, and action items, and that kind of thing.

The terms of reference, I think this probably was one of the biggest accomplishments we had in the meeting. The terms of reference really are a document that supplement the MRA. It's intended to clarify the role of the Joint Sectoral Committee, and give us more specifics about how we're supposed to go about this implementation process. The MRA has a number of things in there that said they're supposed to happen, but very little detail.

So we developed this terms of reference document that talks about responsibilities, the different parties involved, the composition of the Joint Sectoral Committee. As Joe mentioned, the MRA talks about the Joint Sectoral Committee really being two people with two boats, one on the US side, and one on the European side. Two people were not going to get this done. So there's obviously a necessity to expand the committee, which we did.

We talked about participants in the Joint Sectoral Committee. We had a long discussion about this, and agreed mutually that wanted to exclude external parties. We identified some of those as being industry, trade associations, the press.

The focus here was trying to make sure we had a fairly tightly knit group that felt free to communicate openly with each other. We thought that's the keystone of trying to move this agreement forward.

Sometimes some things may come up that might be embarrassing to the other party.

We wanted to limit the restraint on the communication, so that we openly conveyed information, and both sides could make a good assessment, good judgment about assessments we thought that was necessary to limit participants in the group.

We also defined a number of things, work groups as an example. Joseph talked about the safety alert, the recall procedure that's being developed. That's being done by a work group. We have a separate work group set up to look at the common inspection formats.

So these are additional groups that are actually going to come up with the things that we're going to implement to move the agreement forward.

We identified observers. That really was to help, I think, foster broad participation by the member state folks when

we go overseas, to meet, have a Joint Sectoral Committee. Countries who may not have a specific part at the meeting could have observers. It's limited to regulatory authorities as an example, from the member states.

Also experts could attend the meetings. These would be people from regulatory authorities. Generally they participate, are active in the work groups.

Specific responsibilities for the Joint Sectoral Committee were identified, one of the first being communication with the Joint Committee. The Joint Committee is the overall group that is managing the whole mutual recognition agreement. So they're going to deal with telecommunications, recreational craft, as well as pharmaceuticals and medical devices. Communication with that group would be an important part of the Joint Sectoral Committee.

Recognizing we would coordinate activities and monitor implementation of different steps and phases of the MRA, the Joint Sectoral Committee would be responsible for exchanging key information. One of the things that we've accomplished to date is developing a bibliography of laws and regulations as an example that was exchanged through the Joint Sectoral Committee.

Develop a two-way alert system, and ensure operation. The ensure operation part here is a monitoring function. The Joint Sectoral Committee will be responsible for making sure that once an agreement is reached, about how we're going to do that, that it runs smoothly. Making documentation available. We use each other as a conduit for obtaining information about other countries laws, and regulations, and procedures. Agreeing on an inspection report format, which we're working on now.

Clarify the composition of the JSC.

We set up procedures for meetings. We decided that we would meet at least annually, and we would alternate the site between the US, and the European Community. The first meeting was held here, so the next meeting will be held in Europe somewhere, probably in May. Somewhere along there. It'll be about a year from the last one.

We set a procedure for adoption of documents, setting this up as a consensual procedure, wanting agreement on what we did agree to. We agreed to communication to external parties as an example, at the end of the first JSC meeting, we did prepare a public document, a public press release, which I think some of you have. There were some on the chair in the back, and we can certainly make available to you.

Other things we did during the meeting. Confidentiality, as I said, was a big issue. Very sensitive to the Europeans, more so than us. I think we've dealt with it

long enough. We're a little bit more used to it.

But the European folks reviewed European laws. Member state practices vary. They're not the same. Only a few have what would be equivalent to our Freedom of Information Law. We learned that public access to information in Europe is frequently not a right that is enjoyed by US citizens.

Frequently there is no publication of recall information there. FDA, as you know, publishes recall information. The enforcement report is available on the Web site, and that kind of thing. The press also helps us out with those on occasion.

There was a lot of concern about releasability of information. We could see exchanging sensitive documents and we're still discussing exactly how we're going to deal with some of those things.

For our side we reviewed US laws and regulations. We talked about the Freedom

of Information Act, which most of you know, controls release of documents that FDA generates, such as inspection reports. Those of you from inspected firms know that your reports are releasable after some purging.

We talked about the Privacy Act, which deals more with individual personal privacy. Names, social security numbers, things like that. We explained Congressional oversight, which is different for us than it is for them. Already the pharmaceutical MRA I think has been the subject of two very pointed GAO probes about what we're doing, how we're going to implement this.

Frequently the Europeans do not have that kind of oversight. So that's a difference. We also had folks explain our regulations that protect commercial confidential information, trade secret information, and deliberative documents.

Other meeting highlights, we exchanged contact information for both sides.

We set up a monthly phone call that occurs between Joseph and generally Steve Fairchild, to keep lines of communication open. We set up a procedure to establish counterpart contacts between the US and the Europeans as these work groups are set up. As an example, on the report writing format there is a designated US contact for that, as well as a European, so that we can share progress and process on that, and help us move forward in that area.

We agreed to exchange information on investigational training, and invite other parties to those. In the past year we've been able to invite two, up to two representatives per training course from the EU to attend training that we give to our FDA investigators.

Actually this week I think is the second week of a basic pharmaceutical inspection training course that we're having in Baltimore, and there are two people from

the EU that have attended that.

So that again, an effort to try and understand each other's system better, learn from each other, and hopefully move us forward in the equivalence process.

Also made presentations about our alert system and recall systems, and they did, too. We discussed the equivalence process. So, that's kind of a summary of what happened. Again, I think developing the terms of reference took some time, and I think was a good accomplishment. We raised the issue of confidentiality, which we're going to have to deal with, and is going to be a sticky one.

I think set up some good procedures for communication with the other side, with the EMEA, our partners in moving this thing forward. So, thank you.

MR. GAYLORD: Thank you, Raymond, for those meeting highlights. We now would like to give our attention to Brian

Hasselbalch, who is our next speaker. He's a compliance officer in the Division of Manufacturing and Product Quality in the Center for Drugs.

He will give an overview of the evaluation of the pharmaceutical GMP regulatory systems among EU member states, by talking about equivalence assessment.

Brian.

STATEMENT OF MR. HASSELBACH

MR. HASSELBALCH: Thank you, Charles. Good morning. My presentation in the area of equivalence assessments will begin with, if you can stand it, another detailed, a more detailed overview of the MRA conditions regarding this aspect of the agreement. Then I'll discuss how we plan to perform the assessments of the EU member states. Finally, I'll update you on where we are in this effort.

The MRA pharmaceutical GMP's Annex defines equivalence as follows: "Systems are

sufficiently comparable to assure that the process of inspection and the ensuing inspection reports will provide adequate information to determine whether respective statutory and regulatory requirements of the authorities have been fulfilled. Equivalence does not require that the respective regulatory systems have identical procedures."

Now, the key element to this definition of equivalence that I want to highlight is that it applies to systems, and not just GMP requirements and regulations.

To date there are twenty-one EU systems in place for regulating pharmaceutical GMP’s for the various products covered by this agreement. Our long term goal is to assess them all, in addition to the EU directives.

The Annex establishes the parts of a regulatory system that can be assessed in deciding on equivalence. There are seven

major areas of assessment, according to the Annex.

These are, legal regulatory authority and structures, standards of conduct, avoidance of conflicts of interest, administration of the regulatory authority, execution of enforcement activities, effective use of surveillance systems, conduct of inspections, and certain very specific issues concerning pre-marketing approval inspections.

As you can see from criterion one, which I've posted here, and two, the major areas of assessment are often further defined by sub-categories, which I won't describe here. But simply put, virtually every aspect of a regulatory system can be assessed under this MRA.

The MRA also establishes that the final determinations of equivalence are a joint effort, and this has already been discussed. I would like to point out that

this process is expected to be, I think, less deliberative and more determinative.

The Agreement also allows for determinations of equivalence by certain process and product types, which the Agreement leaves to the discretion of either party. Finally, the MRA requires that a finding of non-equivalence be documented to, and reported to, the appropriate regulatory authority.

As to our approach, we intend to be objective, deliberative, and comprehensive. To accomplish this, we've developed a written plan to effect the assessments and the other features of the Agreement. Joe has already summarized the major elements of that plan. I'll add to the details that concerns equivalence assessments.

As I mentioned earlier, the Agreement permits assessments and determinations to distinguish by product and even process types. Which means that it's

possible for us to find an authority equivalent for conducting tableting inspections, let's say, but not equivalent for conducting aseptic processing inspections.

In projecting our workload and resource needs, we identified seven product and process types: solid oral products, non-sterile products, vaccines and biological products, medicated feeds, sterile products, and API's.

Of course, we'll cover all products and process types during our equivalence assessment and documentation reviews. But we'll key in on selected process and product types during the on-site inspection audit phase.

Since we can't evaluate all fifteen member states at the same time, we'll have to choose a priority. The priority will consider such factors as the volume of imports, the number of inspections FDA now

performs in that member state jurisdiction, and the number of manufacturing sites we have registered or licensed in that jurisdiction.

Our aim to this priority is to assess the member states in an order which will give us the greatest possible reduction and total number of inspections performed if that member state is found equivalent.

We will assess the member states in a staggered sequence, such that before we complete the assess of the first member state, we'll have begun the assessment of the second member state, and so on. There will also be three phases to the assessment, which you see here on the screen.

The paper review will be the first phase, and consist of comparative evaluation of the documentation about a regulatory system, again, covering the criteria established in the Agreement. The paper review findings will inform the second phase, which will be an on-site system verification

audit.

Both the paper assessment findings and the on-site system audit findings will inform the third and final phase of our assessment, inspection audits. I might add that we also intend as part of the assessment in the three year transition period to exchange establishment inspection reports. A purpose of that would be to not only build mutual confidence, but to test our system for exchanging that information, which of course, is the currency, the end goal to this whole process.

As to the organizational approach to the assessments, we are making use of technical and program specialists from the involved centers, the Office of Regulatory Affairs, and the Office of the Commissioner, and other FDA offices. These specialists will work together on teams on a part-time schedule.

Finally, our approach has features

that promote our accountability to our public, and to the EU authorities we are assessing. We will communicate to each member state any concerns and questions we have as the assessment proceeds. We'll establish an administrative record of our assessments and our final determinations. We'll publish the list of equivalent authorities in the Federal Register at the end of the transition period.

Before I discuss the progress we've made to date, I wanted to share this work load chart with you to give you a general understanding of how the various phases of the process fit into our decision making on equivalence. I think you have in your packet a photocopy of the real size of this. It's kind of hard to see, I know, from the back.

If I could just point out very quickly, there are basically two phases. The transition period, the end of transition, or operational period. As I've mentioned, the

paper assessments is the first phase. On-site audits, which I've combined here to indicate both the system audits, as well as the inspection audits, are the second and third phases.

At this point we are right here. We have, and are receiving, and I'll go over this a little bit later, EU MS documentation that's under review. Of course, that'll require additional clarification. As we get that, we will at some point generate a report on our findings of that comparative evaluation.

Those findings will contribute to a targeted audit procedure for each member state authority, which will also, as I mentioned, inform the FDA inspection audit. Reports will be generated from that. They will contribute to -- eventually all this will contribute to an Agency decision record on our assessment, and on a finding of equivalence or non-equivalence.

Of course, as has already been mentioned, the equivalence is a joint determination to be made at the end of the three year transition period.

Now I'll discuss our progress to date. This summer a working group comprised of representatives from the involved FDA centers, ORA, the Office of Chief Counsel, and led by the Office of International Affairs, developed a comprehensive bibliography about FDA's regulatory system for pharmaceutical GMP's.

The purpose of this information was two-fold. One, we wanted to initiate the process of equivalence assessment, and provide the EU with the information about our system, for their assessment. Two, we wanted to set an example of the kinds of information we want to have detailing their system, and how we want that information to be organized.

Along with the bibliography, we sent hard copies of each referenced document.

I've lugged them here from my office to show you the kind of volume we're talking about. The information we've provided also serves as benchmarking information about our system against which we will evaluate their systems.

The cover letter for this information requested each authority to provide us with comparable information organized according to the criterion in the Annex. Most have responded with documentation, although some have yet to respond. This letter, as well as our attached bibliography, can be found at our Web site.

You can see how we organized our bibliography, in the slide I have on the screen now, in response to the first criterion as shown here, appropriate statutory mandate and jurisdiction. For example, under 1-A, we identified relevant sections of the Food, Drug and Cosmetic Act. We've provided, although you can't see them

here on the screen, we've provided the URL's or the Web site addresses, for each reference, as available.

The total length of this bibliography is sixty pages. Again, it is posted at our Web site, complete with hyper-link text. By the way, if you take time to review this bibliography, and find that -- or think that there are omissions or mistakes, please don't hesitate to call them to our attention.

To continue then, currently we are reviewing the EU directives concerning pharmaceutical products. We began this review approximately one month ago. We also recently initiated a review of the EU standards of conduct. Recently we commented to the -- for the record to the EU on their recent draft proposal for establishing new standards of conduct. Those comments were not meant, though, to be in lieu of our assessment process. It's still under way.

I'll close my presentation by sharing with you another flow chart describing the basic work process for our documentation review of the information we have received from the member states. This was drafted for the purpose of guiding our work group participants.

Once the evaluation -- well, let me point out again here, we've requested the documentation that's being provided now. We are currently evaluating one part of all the documentation we'll eventually have evaluated, the EU Directives. Once we get to the point of needing clarification about that information, as I'm sure we will, we will make a request to the appropriate EU office or member state authority, await a response.

Continue on until at some point, our review work group is satisfied that they have seen all the information that they need to see, and that they have a complete understanding of the documents provided, and

the system they're evaluating.

Once they're satisfied, they will report their findings to the Project Management Team. Then they'll move on to developing an on-site auditing procedure. Then they'll move on to the next member state.

If the evaluation is for some reason considered unsatisfactory, either because of a lack of adequate response by the member state, or because the information suggests a serious flaw with the system, as it compares with our system, in terms of equivalence.

Then the PMT will help coordinate a response or reaction by the member state. Of course, if -- that may take some time to generate. In which case, the Project Management Team will move on to the next member state assessment.

Finally, I'd like to remind everyone of the existence of an open public

docket for the purpose of sharing MRA related information. That docket number is 98-S-1064. I thank you for your interest and attention, and I look forward to your questions and comments later in the meeting.

MR. GAYLORD: Thank you, Brian. We can see some of the intricacies involved with determining equivalence for the member states.

Now I'd like to give our attention to Sylvia Henry, who is a consumer safety officer in the Office of Compliance and Biologics Quality in the Center for Biologics Evaluation and Research, CBER. CBER is represented on the PMT and the JSC by her. So she's that representative for both bodies. She's going to speak to us today about the development of a two way alert system to ensure the rapid exchange of information between FDA and the EU. Sylvia?

STATEMENT OF MS. HENRY

MS. HENRY: Thank you, Charles, for

that introduction. It's a pleasure for me to be here today to speak on the two way alert system. The purpose of the alert system is to share information in a timely and effective manner in order to alert the public.

Under the alert system, we will be notified of defective products which are potentially life threatening, or could cause an injury to health. It is our hope that this information will be shared jointly amongst the US and the EU member states, so that corrective actions can be carried out in a timely and effective manner.

This information was discussed briefly by Joseph in his overview of the MRA, but bears repeating for clarification of the products which are included, and are not included in the Pharmaceutical Annex of the MRA. For the human medicinal products, this includes prescription and non-prescription products.

For human biologicals, this includes vaccines and immunologicals, but excludes blood and blood related products. For veterinary pharmaceuticals, this includes prescription and non-prescription drugs, with the exclusion of veterinary immunologicals. For pre-mixes, this includes the preparation of medicated feeds for the EC, and type A medicated feeds for the US.

Lastly for intermediates, this would include active pharmaceutical ingredients, or bulk pharmaceuticals for the US, and starting materials for the EC.

For the elements of the alert system, there were criteria that were listed and were taken into consideration for the development of the project. The first being documentation. We took into consideration the definitions for crises and emergencies, standing operating procedures, mechanisms for health hazard evaluations, classifications, language, and the transmission of

information.

For the crisis management system, this would involve the analysis and communication mechanisms, and establishing contact points, and subsequent reporting mechanisms. For enforcement procedures, this would include follow-up mechanisms, and corrective action procedures.

Under quality assurance, this would include surveillance and monitoring of the implementation of the corrective actions taken.

Lastly, for the contact points, the EU and the US FDA have established contact points which are identified for each of the three centers being CBER, CDER, and CVM.

The last point on the previous slide mentioned the establishment of contact points. Both sides have agreed to designated contact points. This will ensure that the information that we’re sharing will be sent to the correct office. The items that are

listed are included in that process.

The alert system itself is being developed into separate components. The first being the recall procedure, which is a joint development to capture vital information that could be considered hazardous to public health. Contact points have been identified in each of the three centers to handle this information. So again, the information that we intend to share will include quality defects, recalls, counterfeiting, and other quality problems. For example, situations such as stability failure, and potency.

For the mode of communication, in order to expedite the receipt of information, and the delivery of information, we agreed to share information using one or both of the following methods: either by FAX transmission or electronic mail.

As with any large project with a magnitude such as this for the MRA, there are

concerns. As being the person who worked directly with the working group, who put together the alert system, specifically the recall SOP, there were several concerns that came out in discussion during our meetings.

The first being language. The concern was receiving documents in fifteen languages, probably from fifteen member states. The second being, if the documents did come in in fifteen different languages, they would have to be translated. So our concern was, how would this affect the urgency and the handling of critical information? Because the information that we're receiving under the alert system is critical?

The third would be the maintenance of records. The problems that could occur if the Agency had to take an action. We wanted assurances that the records are being maintained, and are easily accessible.

Last, we wanted assurances that the

firm could take enforcement actions, if needed. Examples would be recalls, seizures, and injunctions. For this, I didn't want to concentrate on the negatives, which are concerns, but should be addressed, nonetheless. The group made major accomplishments as far as the alert system is concerned.

The Agency's progress to date has been accomplished through the hard work and the dedication of the working group, with individuals from each of the centers who are considered experts in the areas identified for the alert system.

A major accomplishment was the development of the recall S-O-P, which is currently being reviewed by the EU member states, and comments are pending to the Agency. While listening to my co-workers, and listening to some of the things that they were talking about in their presentations, one of the major items I kept hearing was

communication, and the need to establish and maintain communication with our EU counterparts.

I am pleased to say that in developing the alert system, we have maintained regular contact with our counterparts in the EU, and with the alert system in general, specifically the recall S-O-P, we hope to complete the initial phase of the alert system with the appropriate speed, to benefit and protect both the US and EU consumers.

With that said, that concludes my presentation on the two way alert system.

MR. GAYLORD: Thank you, Sylvia for giving us an overview of the two-way alert system. Our final presentation this morning is going to be given by Merton Smith, the Associate Director for International Agreements in the Office of International Programs. He’s going to address public transparency of MRA processes. That is, the

information disclosure requirements regarding non-public documents. Merton?

STATEMENT OF MR. SMITH

MR. SMITH: Thank you, Charles. I too am pleased to be here this morning. I want to mention that my title up until recently was Associate Director for International Agreements. International agreements are so important at FDA that in the re-organization of the international programs, we have created a new staff with several people, that are involved in international agreements now.

Transparency, and the importance of transparency. When we were setting up the agenda for this meeting, we right away recognized that this should be a topic for discussion. I think everyone else on the Project Management Team selected a topic, and sort of by default, this became my topic.

I know, looking at the audience, I know that many of you are very well versed in

the requirements of the F-O-I act. Really, what we're talking about this morning is not only some of the exemptions under the F-O-I act, establishing non-public information. But more importantly, we're talking about a more esoteric, or sort of arcane area of FDA law involving the exchange of non-public information with foreign governments, foreign regulatory counterparts.

As you have heard from several speakers, if this M-R-A Pharmaceutical Annex works out well, we will be normally endorsing inspection reports received from equivalent E-C member state authorities. So conceivably, scores of FDA inspections that are currently done by FDA could, during the operational period of this agreement, then be done by EC member states.

For this reason, FDA believes that it is critically important to make the information that is the basis for equivalence determinations as available to the public as

possible. Indeed, the credibility of the MRA process requires this.

Recently, the FDA was invited to a meeting in Paris, basically to explain our regulatory system. In particular, the Europeans wanted to know how we maintain such good credibility with the wide variety of interested parties that follow FDA activities. Remember, this meeting came on the heels of two important controversies in Europe, the BSE, or mad cow episode, and the dioxins in animal feed problem.

During this meeting in Paris, FDA officials emphasized one key principle that underlies FDA's public credibility. Namely the fact that FDA takes very deliberate efforts to openly communicate with all of its stake holders and that important benefits flow from the resulting feedback.

There are, however, necessary limitations on public openness that are reflected in several pieces of Congressional

legislation. I mentioned the Freedom of Information Act, also the Privacy Act, some other laws, including the Food, Drug and Cosmetic Act, the Economic Espionage Act, and the Trade Secrets Act.

Transparency must be achieved in accordance with these statutes, as well as the regulations that implement their statutes. So I want to spend a few minutes talking about FDA's disclosure rules, and the policies that underlie those rules.

In the next five minutes or so, I will go over FDA's general disclosure policy with -- and discuss and describe some of the important provisions of the Freedom of Information Act that exempt certain types of information from disclosure. Then I'll focus again on how FDA is able to, and in some cases how FDA is not able to, exchange non-public information with foreign government officials.

It is FDA's policy that it will

make the fullest possible disclosure of its records to the public. Such disclosures, however, must be balanced against privacy rights of individuals, balanced against the property rights of persons, such as trade secret information that resides at FDA, confidential commercial information that is property, that belongs to others, that resides at FDA.

Also we need to balance disclosure against FDA's need to promote frank internal policy deliberations. Then, finally, we need to balance FDA's disclosure against its need to pursue regulatory activities without disruption.

Finally, FDA must disclose records except where disclosure is specifically exempted. Now let's look more closely at where the law permits or requires exceptions to full disclosure.

This slide lists the important exemptions for FDA under the Freedom of

Information Act. The so-called B-1 exemption recognizes non-disclosure in the interests of national security. This includes national defense, and foreign affairs. While FDA normally has not relied on this exemption to a great extent, obviously in the area of the MRA, and international agreements, international relations, there is a distinct possibility that we could rely on this in certain instances.

The B-4 exemption recognizes non-disclosure of public -- or, of trade secret information, including confidential commercial information, and confidential financial information. B-5 exemption recognizes non-disclosure of internal government memos and drafts. B-5 is rather circumscribed for FDA, and for other government agencies through some policies that have emanated from the Department of Justice, as well as some clarifications in FDA’s regulations.

B-6 recognizes non-disclosure of information the release of which would be a clear invasion of an individual's privacy. B-7 recognizes non-disclosure of records that the release of which would interfere with law enforcement proceedings, or deprive a person of the right to a fair trial.

Now let's look at how FDA can share non- public information with a foreign government without triggering the requirement to share with the rest of the world. These requirements are part of FDA's regulation, namely Section 20.89 of our CFR, Title 21.

This slide summarizes 20.89. Here I've listed a number of purposes for being able to share non-public information with foreign governments, namely, exemptions should be made to facilitate cooperative law enforcement and regulatory efforts, to pursue harmonization of regulatory requirements, and to implement international agreements.

The last point on this slide notes

that to permit such sharing of non-public information with a foreign regulatory agency, FDA will usually need to enter into a written agreement, or receive a written statement from the recipient government, stating that it has the authority to protect the non-public information and, also, that it makes an affirmative commitment to protect that information.

Now let’s look at some of the detail of what FDA has to do in order to share various categories of non-public information with foreign governments, and then not trigger the Uniform Access to Records Requirement that I mentioned.

First, for law enforcement records that are open or ongoing, there’s no requirement for FDA to receive a statement from the foreign government that it will -- that it has the authority, and will protect this information. However, FDA does transmit this kind of information to foreign

regulators with a cautionary letter that advises those regulators of the need to keep this information; -- to non-disclose this information.

For records containing confidential commercial information, FDA needs a statement that the foreign government has the authority to not disclose the information, and also a commitment that they will not disclose it.

Furthermore, FDA often needs the consent of the submitter of the confidential commercial information. Although if we feel that it's in the interest of public health to share this information, we may not need that consent, for confidential commercial information.

I wanted to note to this audience, and when we go to the question and answer period, FDA is really looking for a reaction to the problem that we have of having to deal with getting consent, particularly from the industry, to share confidential commercial

information, as well as trade secret information, with foreign governments.

Rather than do this on a case by case basis for every piece of information that we have to share under this agreement and other agreements, we're looking for ideas from the audience about whether we could have some sort of blanket agreement with an industry that has this kind of information that we want, or that we may have to share with under these agreements.

So, if you could give us some feedback, either during the question or answer period, or send written comments to the docket that Brian mentioned, we would appreciate it. We're looking for ways to make this exchange more practical for FDA, without jeopardizing industry's rights, property rights.

Finally, for records containing confidential commercial information that are shared with visiting foreign scientists on

FDA premises, we have to get, we want to get, and we have to get a signed statement from the visiting scientist that they commit to not disclosing this information. Also, we need to get a statement saying that they have no conflicting financial interest in the information.

For records containing trade secrets that are shared with foreign governments, in this case, FDA requires a statement of authority and commitment, but also needs the property owner's consent. Again, we're looking for ways to avoid having to get that consent on a case by case basis. So, any ideas that particularly members of the industry have in how we could do this would be appreciated.

For records containing trade secrets that are shared with the visiting scientists on FDA's premises, FDA requires again, a signed statement committing that they will not share this information. We

don’t allow them to take this information away from FDA, obviously. But they have to sign a statement saying that they commit not to share it, not to disclose it and they also commit that there is no conflicting financial interest that they have.

For records containing pre-decisional information that is shared with foreign governments, FDA requires a statement from the foreign government that they have authority to not disclose this information, and also a statement that they commit not to disclose the information.

Although in 1998 FDA published a proposal that would eliminate this requirement for pre-decisional information. we are about ready to publish the final rule. So there’s a chance that this requirement could be eliminated.

However, FDA, for pre-decisional information, we do have internal FDA procedures that assure that there’s no

improper pre-decisional information that would be shared with foreign governments.

Finally, for records containing personal privacy information, again, FDA generally requires a statement of authority and commitment, as I've mentioned before, for other types of information. But we also require, generally, that the individual give their consent to disclose this information.

In conclusion, while FDA strives to be as completely transparent as possible, there are certain limitations that reflect legitimate public policies. Namely the protection of public rights, or property rights. The protection of privacy rights.

A need by FDA not to chill the documentation of spontaneous internal Agency deliberations. Or not to chill or circumvent regulatory -- FDA's regulatory pursuits. As I explained, that generally if FDA shares any non-public information with a foreign government, it must share it with the general

public. This is, again, under 20.21. It's called the Uniform Access Rule.

But if we follow procedures outlined in 20.89, where we have certain safeguards, FDA can share non-public information with foreign governments without triggering this Uniform Access to Records Requirement. Every day as part of FDA increasingly frequent international cooperative efforts with foreign counterpart regulatory agencies, the FDA finds it increasingly necessary to exchange non-public information with its foreign regulatory colleagues.

I look forward to any questions that you might have about this. I note that we have some experts from our General Counsel's Office, and other offices that deal with Freedom of Information. The exchange of information with foreign government counterparts really doesn't fall under Freedom of Information. But obviously from

what I've said, there are implications for Freedom of Information.

Thank you very much.

MR. GAYLORD: Well Merton, we'd like to thank you as well, and each of the presenters this morning for providing us with that information.

At this point, we'd like to take a fifteen minute break, and come back to the second part of the meeting. As Sharon mentioned at the outset, this is a dialogue. So, when we come back, we'll have presentations from the audience, followed by the Q and A part, which I know that you are waiting for.

We like your input, and look forward to those parts. So, we're going to re-convene at twelve minutes of by this clock here.

(Recess)

MR. GAYLORD: As I had indicated at the outset of the meeting, there were three

who were going to be in attendance today who said that they would like to give presentations. I saw two of the people on the sign-in sheet. I'd like to know if Ms. Doris Haire or Ms. Sybil Shainwald is here, from the National Women's Health Alliance? They were one of the presenters. Are either one of them here today? I know Doris. I didn't see her.

So, well, they may have stepped out. I'd also like to acknowledge the problem with parking that some of you may have faced. Most people when they called said that they were going to take the subway, but I know a fair number drove. So, some had to go out to feed the meters, or to move their cars. I apologize for the tight parking space situation here. It's something that as FDA'ers we've endured for a while. We hope that you were able to get your cars to safe haven. We have the parking lot, but it fills up pretty quickly, the pay parking

lot.

One thing, too. After the presentations, we will have the question and answer period. as I mentioned before, you can write your questions down on the index cards that are in the packet. We have people that will collect those. So, if you can pass those down. whoever on the end of each of the rows, if you would just hold those up.

Erik Henrikson, or Nancy, or others that have volunteered, said that they would pick those up, we will relate those.

Well, to give our first presentation, we have with us from the Consumer Health Care Products Association, Mr. William Bradley, who is the vice president for technical affairs. So, let’s give our attention to Mr. Bradley as he gives our first presentation.

STATEMENT OF MR. BRADLEY

MR. BRADLEY: Thank you, Charles.

Originally, these comments were going to be given by Dr. Frank Sena, who is chairman of our Manufacturing Controls Committee. But he was called to jury duty. Therefore could not be here. So, I'm going to be presenting these comments for him.

My name is Bill Bradley. I am Vice President for Technical Affairs for the Consumer Health Care Products Association, CHPA, which was formerly the Non-Prescription Drug Manufacturer's Association, which more of you are probably familiar with at this time.

CHPA is a national trade association that has been representing the manufacturers and distributors of non-prescription or over the counter OTC drug products for over a hundred years.

I would like to take this opportunity to state that CHPA strongly supports the MRA effort, and the proposed rule, with its potential to improve patient

access to safe and effective technologies, reduce unnecessary regulatory redundancies, enhance the access of United States and EC companies to each other's markets, provide significant savings to both companies and regulators, and set the stage for further regulatory cooperation and harmonization.

CHPA believes that the proposed rule and the MRA allow for incorporation of the best regulatory attributes of both parties. CHPA supports the FDA view that equivalence of GMP reports, and other conformity assessment reports and evaluations between the FDA and EC member state authorities and CAB's can be relied on to help ensure the safety, quality, and effectiveness of products exported to the United States while also reducing the regulatory burden on manufacturers.

CHPA hopes that the MRA and the pending regulation also permit FDA to re-direct some of its inspectional resources

from countries whose systems are found equivalent to or higher than risk priorities not covered under the MRA. I'm sorry, that we hope they can re-direct some of it to risk priorities not covered under the MRA.

The Agency may thus better target its limited foreign inspection and other resources devoted to imports and other regulatory concerns. Thus, FDA will be able to leverage its resources by relying on information from its counterpart regulatory authorities in foreign countries that have demonstrated equivalence.

CHPA anticipates that under the MRA and the proposed regulation, as equivalence is achieved between regulatory systems of EC member state authorities or conformity assessment bodies, and FDA, there will be reduced need for importing countries to engage in resource intensive foreign inspection, sampling, and examination of products being considered for entry from

countries with equivalent systems.

This can assist in speedier approvals of safe and effective products, and in more comprehensive and effective surveillance of GMP's and quality systems. We support the transition period, with its emphasis on collaborative confidence building activities between FDA and EC member state authorities, and CAB's which should result in harmonization of requirements at a high level of consumer protection, thus enhancing regulatory controls.

CHPA also urges FDA to consider and ensure the continuance of the US system for the approval, manufacture and compliance programs associated with OTC medicines. Few countries within the EC maintain a class of quality drug products equivalent to the US OTC industry. Hence, the compliance approach within the EC should be to treat OTC as Rx-products.

A clear example of the difference

in compliance evaluation in the US is the longstanding FDA exemption from expiration dating for non-dosage limitation OTC's for which the manufacturer has greater than three years satisfactory stability support. This type of exemption does not exist in the EC.

CHPA is also concerned that the language of the proposed rule published on April 10, 1998, refers almost exclusively to marketing authorizations, licenses, et cetera, which are terms usually applied to our ex-products or, in the EC, registered pharmaceuticals, and may not be associated with OTC products.

Finally, CHPA would also add its encouragement to the efforts proposed by FDA during the transitional period, designed to build joint confidence between the parties through seminars, workshops, joint training exercises, and observed inspections.

Furthermore, CHPA offers its membership to assist in this effort in any

reasonable way that FDA may judge appropriate. Examples of such assistance could be hosted joint plant tours, or participation, or contributing faculty to inspectorate training, or workshops.

Thank you for the time and opportunity to present these comments.

MR. GAYLORD: Thank you, Mr. Bradley, for presenting those comments for us today. Now I'd like to give our attention to Ms. Mary Bottari, of "Public Citizen". she is the director of their Harmony project, Harmonization project. She is fresh back from Seattle, and so is still recovering from that. But it is a pleasure to have you with us Ms. Bottari?

STATEMENT OF MS. BOTTARI

MS. BOTTARI: Thank you very much. I am the director of "Public Citizen's" Harmonization Project. what the Harmonization Project does is we track international harmonization activities in all

federal agencies, and we try and examine the harmonization impact upon consumers.

We are also part of the Steering Committee of the Trans-Atlantic Consumer Dialogue, and so have been following this MRA with great interest, and was very interested in the presentations here today.

We are basically a little uncomfortable with this mutual recognition agreement for a wide variety of reasons. But I'll make my comments brief. It's very concerning that the MRA was discussed as early as 1989. Yet prior to it being signed, there was very little public notice, public involvement, in the MRA process.

We are also concerned that the MRA will be privatizing what are normally public health functions of the US government. We are concerned that EU manufacturers can pick and choose amongst CABs and that as a 1996 GAO report made clear, that the notified bodies in Europe operate under much less

comprehensive conflict of interest standards than our FDA officials do here.

"Public Citizen" has a wide variety of interests in these types of issues. But most importantly to us are the impact of these trade negotiations on four of our most treasured laws: the Freedom of Information Act, Administrative Procedures Act, the Government and Sunshine Law, and the Federal Advisory Committee Act, which require balanced advisory committees in the government.

There’s been a lot of discussion here about transparency and confidentiality. These continue to be controversial topics in negotiation of the MRA. for those of you in the room that think the FDA is persnickety about this stuff, they’re not half as persnickety as we are.

We want to ensure that all government documents that are currently available to consumers will remain available

to consumers during the implementation of this MRA. That means all inspection reports, all recall alerts, and a variety of other documents that will be generated.

When we hear from Merton Smith that the FDA could possibly invoke a national security exemption to the FOIA, that alarms us. It's hard to imagine what the national security implications are of this type of pharmaceutical agreement.

We're also uncomfortable with the notion of equivalency. The notion was created in the World Trade Organization as sort of a wishy washy notion that doesn't mean that you have to harmonize specific standards. That you can take whole sets of regulatory, perhaps very disparate regulatory rules, and just sort of declare them equivalent.

US federal agencies have been reaching different equivalency agreements. They haven't been defining their terms. They

haven't been defining what criteria they use to reach equivalency. The FDA is doing a slightly better job than other agencies by defining different criteria they would use in reaching equivalency determinations.

But we would hope that when you get to the point where you are going to make an equivalency decision, that you will post that as a proposed rule. That you will list every single criteria examined, and the performance of the other nation state on those criteria.

Of course, we would hope that the FDA is going to be maintaining or improving the current level of public health and safety achieved under our US laws. We would ask that once an equivalency decision is reached, that there is a mechanism for an ongoing review of the equivalency decision. That after three years or five years, there is again, public record of rule making on the equivalency decision, to make sure that it's working for US consumers.

Lastly, the FDA has often stated that its resources to engage in these kinds of activities are stretched thin. We would hope that the FDA would be able to secure the resources needed to make sure they pursue all these international trade activities in the most appropriate manner guarding US public health. Thank you.

AUDIENCE QUESTIONS

MR. GAYLORD: I'd like to thank you, Ms. Bottari. We appreciate that input. We're glad that at least one consumer group was here. We know that many were in Seattle. So we appreciate your being here today.

I'd like to ask again if the National Women's Health Alliance is here. It's one of the consumer groups, and they wanted to present, as well. If not? Then we will proceed to the convening of the panel, so that we can have the Q and A discussion.

We'd like to have our attention directed again to the project management

team, that will comprise one panel. In addition, we have representatives from each of the organizations, the centers and other offices that have been involved in the implementation, as well as the negotiation of this particular agreement.

So, for the second panel, we have two directors from the Office of International Programs. We have Walter Batts, who is the Director of the International Relations Staff. I'd like you to come forward. We've had your name, plaquard for you there. I know that Linda Horton was here earlier. She will be back very shortly, okay, and will join us. She's the director of the International Agreements and Trade Staff.

As Merton mentioned to you, there is an organizational change within the Office of International Affairs. There are now going to be sub- offices under the Office of International Programs. So, Linda Horton and

Walter Batts are two of the directors of the four staffs.

In addition we have, in our audience, we have representatives from the Centers. The Center for Biologics, we have Dr. Elaine Esber. I see her in the audience. We have, from the Center for Drugs, we have Stephanie Gray. I saw, she is here. Also, we have from the Office of General Counsel, we have Miss Leigh Hayes. We have Katherine Cooper, who is a recent addition to the Project Management Team. So, I would like to welcome each of them.

At this point we are going to throw open this part of the meeting to you in terms of questions that you might have. We ask that you use the microphones that are on each of the outer aisles. Again, if you would give your name and organizational affiliation, we would appreciate it. Again, if you have any questions that you've put on the index cards, you can pass those to the

outer aisles, and they will be collected and forwarded.

So, who would like to go first. Yes, please?

MR. FREY: I'm Ed Frey, and I'm with the EA, which is an international association pharmaceutical scientists. I noted what Joe Famulare said, that the MRA is not a harmonization process. I appreciate that. It's about equivalence determination.

But it seems as if it will not fulfill its promise without -- without attention being given to harmonization of the requirements that underlie the very purpose of inspections. The situation the way it is now, companies who operate in various regions of the world face different requirements for sterile filtration, different environmental monitoring requirements for new technologies.

Example, barrier systems for aseptic processing. Different rules for media fills. The implementation of Part 11,

the new FDA rules for electronic identification, electronic signatures. Possibly even the very definition of GMP itself.

There is a player that has not been mentioned, the Pharmaceutical Inspection Convention/Cooperation Scheme, which is producing GMP requirements that appear to be adopted by the European Union authorities without a public participation process. I wonder if the panel has given any thought to the impact of this. What is the thought about the importance of harmonizing, so that the inspections really do report on the same things, and apply the same requirements worldwide.

MR. GAYLORD: Joseph?

MR. FAMULARE: Your question is loaded with many aspects in determining equivalence. First of all, I'll start out with the whole concept of harmonization.

While harmonization is not at the

core of this Agreement, its equivalence, as we well emphasized, the fact that regulatory authorities now as part of this process are coming into collaboration and working together, there are certainly holes.

There's certainly no prohibition against certain harmonizations taking place. I think it's just a natural outcome of the process.

So certainly, as we look at evaluating each other's standards, there may be differences in standards, whether it be for aseptic filling, media fills, or laminar flow hoods, and so forth. These other technical areas where there may be differences, it remains to be seen as a result of our equivalency assessment process if we can live with those differences.

Or whether, for example, an authority or an area is found not equivalent, if they're found so -- to be disparate and harmonization in those areas, or some meeting

of the minds will occur.

So these are things that are yet to play out in terms of how those things will be evaluated. Just bear in mind that what holds it does hold, that some things that are not exactly the same will be deemed equivalent and maybe some things will be deemed so different that they cannot be equivalent. That may move both sides towards some sort of "harmonization" on those efforts.

The other point you brought up was, for example, Part 11 was one other point you brought up. We have a rule in place here. The Europeans have their ways of dealing with the electronic records and signatures and again, just like the GMP's or other directives, guidances, and so forth, whether they emanate through rule making processes in each authority at the EC level.

Or if something is adopted as a result of PIC influence, we will have to look at and evaluate if it's equivalent to our own

process. Our process, of course, any guidance, or directive, or regulation that comes forward, we have standard procedures for sharing that with the public.

Whether the European authorities are bringing into place directives or guidances that aren't going through that process, whether it be through PIC, or some other means, we will look at that against our own. We are looking at our laws, directives and regulations as bench marks, to compare to theirs.

Remember that we're looking at their overall system for evaluation. So it looks at how they put together their laws, regulations, how they enforce them, and so forth. So, these things will be encountered as we go through our equivalency assessment process.

They may slow things down. They may cause problems. They may cause bumps in the road as we go along. These are things

that we have to consider, and important factors, as you pointed out in your question.

MR. GAYLORD: Would any of the other panelists like to address that question?

Okay. I'm going to read one of the questions that was just passed forward. It's a three part question. Raymond had mentioned about GAO had at least two pointed inquiries that they directed to FDA.

So the first part concerns GAO. It says, GAO has expressed concern about FDA's MRA implementation. What are GAO's current concerns? What GAO concerns have been addressed? What are the potential impacts of GAO's ongoing concerns on the implementation time table?

So, who would like to address that? For those who give responses, if you would give your name, so that that can be recorded for the transcription process. Raymond?

MR. MARS: Is anyone from GAO here?

You get an answer, so I don't know. I'll have to be careful.

I've been in this process for about a year. What I've seen really are two focused probes. From my perspective, the probes are focused at the procedures we're going to use to assess equivalence. They're also interested in a plan, and time table, and things like that.

I think FDA has assuaged that concern pretty well. We have a very detailed plan for progressing and taking specific steps to move forward. We've given you a summary of that.

The other part of it has to do with the actual criteria we are going to use to make those equivalence assessments, as well as some concern about the order in which we're going to deal with the countries. Our responses to GAO have basically been that, in stepping through the plan, as we've developed it, that we will develop criteria that we'll

use to assess each of the fifteen member states, and all of the regulatory systems.

It will be a common approach. It's going to be kind of an iterative process that we anticipate is going to be completed with the first assessment of the first member state. Brian laid out some of the criteria we're going to use to determine who we're going to do first.

But you know, that's basically where I've seen them questioning us. The other issue has been resources. Have we got the resources to do it? Do we have the expertise to do it? Some of that I think we've answered. We do, FDA does in some other areas domestically, within the state program, milk program and some others, we do make equivalence assessment of other regulatory systems.

So it's not an area totally new to us, although doing it overseas certainly is. So it's been, the specifics of the

implementation program, resources, that kind of thing.

MR. GAYLORD: All right. What about potential, in terms of the -- Brian?

MR. HASSELBALCH: Brian Hasselbalch. If I could just add to that. That was a very good summary of GAO's concerns. The two outstanding in their most recent report were the order of member states, and the lack of values assigned to equivalence criteria. Such that, could we consider a particular element to a system so critical that, absent it, we'd find them not equivalent at the outset, and so on?

So of a system of critical major and minors. You're very familiar with the sampling plans. As Ray mentioned, we understand the need for that kind of an approach. That is the approach we will take. But we didn't have answers for GAO in accordance with their time line or table for needing answers.

But I think we satisfied them that that is how we are thinking. We'll develop a more detailed procedure for that in the future. As well as the establishment of the order of member states.

So I think GAO's concerns were largely a result of a difference of opinion on the timing for that information, rather than the need for it.

MR. GAYLORD: Sylvia?

MS. HENRY: There was also some concern from GAO regarding the Gant chart that was provided. The Gant chart is a line by line listing of the activities which are involved in the MRA process itself. we provided answers to the questions that came up from GAO on that.

MR. GAYLORD: Okay. All right. We're going to ask one other question from this, and then we'll go to Dr. Wood.

The Canadian authorities issued an SOP describing processes or procedures they

will use for joint inspections. Will the FDA give industry similar guidance on US - EU accompanied inspections?

Secondly, can industry assume the process for the US - EU MRA will be similar to that described in the Canadian SOP?

Raymond?

MR. MARS: Ray Mars. When we get to the point of doing on site inspection equivalence determinations, I think what we foresee is accompanying the member state inspector, after reviewing their procedures, and policies, and that kind of thing, and observing what they do.

We will develop measures that identify probably critical things that we think need to be done on an inspection. But I think it’s going to be very similar to what we’re doing now with the Device Certification Program.

Basically, we’re along to observe how the other person does what it is they’re

doing. then to make a judgment of that, to determine whether or not they're doing an equivalent job in terms of inspection. Again, it's not going to have to be identical to the way we do it. But some equivalency of critical areas.

MR. FAMULARE: I might just add on, I think the concern there on the question is the -- will industry know what's going on? We've discussed on both sides, from our side and from the European side, that we would try and keep industry appraised of our plans on how we're going to go about these joint inspections.

Because there's been concern raised. Well, will it be a, you know, one topping the other type thing? No. We want to make sure that the folks that do these assessments are trained in the assessments on our side, and the Europeans on their side, in terms of doing an inspection in a normal manner that could be observed by the other

side.

MR. GAYLORD: Would anybody like to address that? Okay. Dr. Wood, please.

MR. WOOD: I'm Richard Wood. I'm the director of Animal Concerns Trust. We're a consumer group that works on food animal issues. I have a question that you've really touched on, I think, but I want to see where it fits on the flow chart.

The regulation states that the FDA will make available in a public document the complete administrative file that constitutes the basis for the FDA's equivalence determination. So Dr. Brian Hasselbalch, you laid out the flow chart. Where in that flow chart might we expect that report to come, then?

Would it come out as one assessment, equivalency assessment is completed, and then we'll see a report? Or what might we anticipate as we look at this?

MR. HASSELBALCH: Brian

Hasselbalch. The timing of that, as I indicated, albeit not clearly, would happen at the end of the transition period, that is, at the end of the three year period. We don't intend to issue reports of our finding of equivalence or non-equivalence until the very end.

MR. WOOD: So even though in the flow chart, under the transition period, where it indicates there's FDA assessment findings compiled in the report, and so on, that would not be -- those kinds of -- that public report would -- at that point, then, would have to wait until the end, is that right?

MR. HASSELBALCH: Right. That information at that point wouldn't be publicized. Again, those are findings of assessments, many pieces to the overall assessment that get compiled, and put into an Agency decision making record, which would be the decision point on equivalence or

non-equivalence. Or no finding can be made because of a lack of information.

MR. WOOD: Just so that I'm clear, and I apologize for belaboring this a moment. But then the only point at which the public will be able to really see the full status of these assessment findings will be after the assessment has been made then, is that correct?

MR. HASSELBALCH: That is correct.

MR. GAYLORD: Yes? Please?

MS. WEXLER: I'm Jill Wexler, with Pharmaceutical Executive magazine. As I understood from Dr. Hasselbalch's remarks, the current procedures is that you're looking at certain member states first, and others later. that you also may look, focus your equivalence assessments on certain kinds of products or processes.

Is this procedure, the modus operandi agreed on by the EU? My impression was initially that they were looking for sort

of an all or nothing Agreement.

MR. HASSELBALCH: The product process distinction is of course, agreed upon. That is enshrined in the Agreement. You're correct, the EU is concerned that we finish all member states, all systems, in the three year transition period established in the Agreement.

The Agreement of course, also has language which allows either party to make as diligent an effort as possible, given their existing resources, to complete the effort. It doesn't actually require that, the assessments, the language of the Agreement, to our read, my read, doesn't require that assessments be necessarily finished at the end of the three years.

But the EU did indicate to us in our last meeting that they felt if we couldn't finish them all by the end of the three years, to a determination, then we'd have to extend the transition period,

effectively. Move it beyond three years. thus, delay any benefits that we might otherwise get from a finding of equivalence.

Which would be an exchange of inspection report for normal endorsement. A cessation of inspections for those equivalent authorities, and so on. So, we're still discussing that. We have a difference of opinion on how the Agreement obligates either party in that regard.

MR. FAMULARE: That's why I emphasized in my presentation that although we have a plan over this next three years, that plan is subject to the availability of resources, and other factors beyond our control, in getting done with the member states by the end of the three year transition period.

MR. GAYLORD: All right. As I mentioned, there's a three part question, and I'll ask the third part of this question that's stated on the first card I received.

It says, does FDA see piecemeal implementation as possible or likely? Now, there's a definition of piecemeal here, and I cannot make out a portion of it. But it says, piecemeal means a member state could be found equivalent for tablets, not for something dealing with production.

Then it says, is piecemeal absolutely out of the question? So, the author of this question, if you'd like to elaborate further before this is passed to the panel? Yes? Please?

MR. McMILLAN: -- aspect of their production, their equivalent. There is equivalence in other parts -- we can proceed.

MR. GAYLORD: All right. your name and organizational affiliation?

MR. McMILLAN: Steve McMillan -- American Pharmaceutical --

MR. GAYLORD: Okay. Mr. McMillan. Thank you. We'd like to address that question.

MR. HASSELBALCH: I'll address it. Brian Hasselbalch again. Yes, we would proceed. In fact, that is my understanding of the negotiation process. The development of the language of the Agreement was that that particular element of the Agreement was put in for the most part to allow us to move forward to a potential finding of equivalence, even though many member states couldn't or don't regulate active pharmaceutical ingredient production.

But of course, it includes not just API's but all product and process types, any product and process types. So, it's a feature of the Agreement that allows us to carve away from, or carve out, problem areas, or areas of major disagreement, so that we can move forward to a finding of equivalence for other areas where equivalence exists.

MR. McMILLAN: (Inaudible)

MR. HASSELBALCH: I'm sorry? It's possible. Until we actually get further into

the reviews, you know? My guess, yes. It's very likely. Certainly for API's, at this point. If I were to --

MR. FAMULARE: Joe Famulare. I might just add to that also, from the European perspective. They also looked at that feature, because they realize that not every of the fifteen member states for example, may have expertise in every area of production.

There may be authorities that don't even have facilities that produce sterile products. So that's another encumbrance that's overcome by this parsing out of processes.

So there's two ways of looking at it. One, a process may exist in a member state authority that is not found equivalent after our review.

The other way of looking at it is that a particular -- when we give an authority, when we say an authority is found

equivalent, if they don't even have the capability or expertise in that area, we certainly wouldn't say that they're equivalent in small volume parenteral production.

Then three years later a plant opens up, and we've never assessed them for that particular technical aspect.

So that allows a number of flexibilities. That's why that's worked into the Agreement.

MR. GAYLORD: Anyone else? Merton?

MR. SMITH: Merton Smith. I'd like to just clarify that if we do this piecemeal at all, you don't necessarily infer that where we have not determined equivalence that there's a problem with their system. It may be a problem with getting the information about their system, or some other problem.

Not necessarily that we're finding them non-equivalent, and trying to work on that. That's the delay. So, I just wanted

to --

MR. GAYLORD: Okay. Anyone else from the audience would like to ask a question? Would you please use the microphone? So, whenever you have questions, please, if you'd go to the microphones, we'd appreciate it.

MR. HOLMES: Malcolm Holmes. I chair the Working Party for the EFPI Committee on MRA's, the European Federation of Pharmaceutical Industries, and also work with Glaxo-Wellcome.

I'd just like to take up on the issue of API's, which is something I see where perhaps there could be non-equivalence stated, because the legislation isn't in place in much of Europe to actually cover API's at this stage.

I wanted to know what the process would be for including those API's post the transition phase. Because many countries will actually have legislation in place

probably towards the end of the three year transition period.

MR. HASSELBALCH: Brian Hasselbalch. The specific details of post-transition operational period management of the Annex, joint management of the Annex, haven't been decided.

But we have talked basically that the equivalence assessments would of course, make a finding, or the assessments would arrive at a finding of equivalence, or non-equivalence, or lack of information. It would be stated and reported to the EU, as well as the involved or affected member state.

It would be up to them at that point, then, to re-initiate our review of their system, or one or more aspects. Whatever the glitch is, we'd re-visit it. It would be prompted by, I guess in short, the member state making a request, or providing us with the information that remains

outstanding. So that we could continue on the review in that area.

MR. HOLMES: There is a mechanism which would allow this to take place post the completion of the transition phase.

MR. HASSELBALCH: The Annex doesn't describe such a mechanism.

MR. HOLMES: I know.

MR. HASSELBALCH: But we intend there to be such a procedure, or an allowance for that. In other words, we don't intend that, just because somebody's found non-equivalent, or that we have a lack of information to make a finding of equivalence or non- equivalence, that that's the end of it for that member state, or that authority.

We intend that there's a way for an authority to resurrect the review with the FDA. We hope that that would work in reverse, also.

MR. FAMULARE: Joe Famulare. If I could just add, we really don't find somebody

non-equivalent. If we really come to a point where we cannot find equivalence, we report back to that authority, and the EC. As Brian said, "These are the problems."

Then, it’s up to that authority to come back. Of course, with the hope that any authority would be able to answer those problems, questions, or come up to the -- or find the ability to come up technically, or whatever the problem might be, to then come to a finding of equivalence.

That’s why we said at the end of the transition period, we will list those authorities which are found equivalent. The other authorities that you don’t hear about, either we didn’t get to yet. Or we’ve reached that point where we had to report back, we are not finding equivalence because.

MR. HOLMES: I think this might well be a point, though, where there will be an early recognition from all parties that because legislation isn’t in place, then

equivalence can't be there. Therefore, just looking at the way forward for that process, when the Europeans are working towards putting legislation in place, perhaps the same legislation via ICH.

MR. FAMULARE: Well, of course, when we've already broached that subject, even in terms of what products will be included in alert system exchange. Whether or not API's can be included in the exchange if there isn't legislation in place in member states for API. So it's an issue we're already broaching.

MR. HOLMES: Thank you.

MR. MARS: This is Ray Mars. If I could add to that just a little bit. I think I was reading into your question whether or not there would be a continuation of an assessment beyond the transition period. I think even the MRA talks about re-evaluating radio pharmaceuticals, and some other products that are excluded during the three

years.

So, I think the anticipation is there that the assessment process will continue, even once we get into the, quote "operational" phase.

MR. GAYLORD: Mr. McVicar?

MR. McVICAR: Thank you. My name is William McVicar. I do a publication on recalls, regulations, and so forth.

I'm particularly concerned about Freedom of Information, not only for my own purposes, but also many government agencies routinely release information such as consent decrees, court decisions, such as from the Justice Department. Even FDA releases recalls, talk papers.

Now, my question is, not even getting to Freedom of Information, which is going to be very difficult, but these routine things which the public has come to expect. Are we going to move in the direction of Europe, where these things are not discussed,

not released?

Or are they going to have to move in the direction where some things adverse are routinely released?

MS. HENRY: I'll speak directly on the alert system itself. That was one of the concerns in developing the working system and the fact that, in the US, we're very concerned with alerting our public of potential dangers to health.

For the recall information that will be released, it's the same information that's seen in the FDA enforcement report. It includes things such as the firm's name, the reason for the recall, the consignee, whether or not we've received contact back from the consignee. Any follow up mechanisms, and corrective action.

But as far as the alert system is concerned, we are working jointly to make sure that all information will still remain available to the US consumers.

MR. McVICAR: Is that all information concerned with foreign firms?

MS. HENRY: That will be the exchange of all information related to recall that the FDA is made aware of, the classifications being Class One and Class Two.

MR. McVICAR: That FDA is made aware of.

MS. HENRY: Right. FDA expects to be made aware of, in a timely manner, Class One and Class Two recall notifications. Class Three notification actions are not as severe. They do not cause an injury to health. They don't cause potential death.

So that information will be received, but it won't be received in a timely manner, as what we would receive with Recall Classification One and Two.

MR. McVICAR: I want to commend FDA. This is a very difficult assignment. Lots of luck.

MR. GAYLORD: Joseph?

MR. FAMULARE: I just wanted to add to your overall concerns, in terms of FDA releasability of information. We've already stated when we published our rule that we intend to treat EIR's that we receive, and normally endorse as we would our own, in terms of Freedom of Information.

We're looking with that view overall on all documents that FDA maintains, that are obtained, to the degree our laws allow releasability now, in general, we will continue to handle those documents in the same manner. In terms of, if we use them to make a regulatory decision, then the public is entitled to them as if FDA generated the documents on their own.

MR. GAYLORD: Any other panelists like to addressthat? Linda?

MS. HORTON: About inspection reports. There also is a sensitive issue of FDA's assessment of a foreign country's regulatory system. At the point where FDA

makes a finding of equivalence, there will be made public a summary of the basis, as we promised in our rule making.

During the preliminary stages, however, I think people can understand there's a great deal of sensitivity about looking at other country's systems. Particularly when there still is some work to be done. So there is -- there is that issue that we're working on with the Europeans, because it would inhibit candor and in the deliberative process if there were premature disclosure of information of that nature.

But we're committed to a transparent process, and the implementation of the MRA.

MR. GAYLORD: Merton?

MR. SMITH: Merton Smith. I'd like also to add that the issue of transparency, as I said in my remarks, we found our transparency at FDA to be valuable in protecting the public health. The feedback

that we get from interested parties is critical in that.

As part of the equivalence assessment of each member state, we've stated that the criteria for doing that assessment will include the transparency of the member state system. So we will be assessing the equivalence of their transparency within the member states. So we'll have to -- obviously there's no way to avoid these issues at all, not that we want to.

MR. GAYLORD: Mr. Frey, before we take your next question, I'd like to read one from the index cards. This is from Mary Bottari of Public Citizen.

"Will the FDA notice any equivalency decision as a proposed rule and allow public comment on a country by country basis"?

MR. FAMULARE: If I could take on that question. Our intention is to put the notification of equivalency in the Federal

Register, but not as a proposed rule. Realize that the docket is open at all time, the docket number that has been mentioned already, for us to obtain any comments from the general public, industry at large, et cetera. Any interested parties, of any information they may have bearing on the equivalency of any particular member state, or the overall process.

So that process is open for public input. As Linda Horton said, at the end of the process where we find an authority equivalent, we intend to make our record open as to what the basis was for finding that equivalence.

MR. GAYLORD: Linda?

MS. HORTON: If I might add, nothing in this MRA changed any FDA requirement. Furthermore, we were adamant about our need to go through notice and comment rule making on the MRA itself, it probably was not strictly required. But we

felt that this was such a significant public policy that to be on the safe side, we should do rule making on the MRA itself. There is not a need to go through an individual country by country rule making for each individual European country, as we continue the implementation of the MRA.

MR. GAYLORD: Mr. Frey, please?

MR. FREY: Thank you. Ed Frey, PDA. Just a quick question for Sylvia Henry. I may be jumping ahead too far, but what effect does the information exchanged in the alert system have on the status of NDA and BLA approvals and supplements? Specifically, in order to interrupt or suspend the approvability of supplements and applications pending before FDA, how much information do you have to have from abroad?

MS. HENRY: Well, with the alert system itself, and with the mechanisms for the information we expect to exchange, it could impact. Because if we find out, in

particular, usually with manufacturing facilities, if there's a problem in one particular area, there may in fact be problems in another.

That information could alert other individuals who are responsible for conducting the review of BLA's that problems could exist. It may not delay the process. But it would give the Agency more information to go on.

MR. FAMULARE: If I might, this is Joe Famulare. If I might add, one of the things that we're realizing is that we publish all our recall information already. I mean so, it's no, from the European side, it's nothing new, other than maybe some earlier notifications, than when it actually goes into the enforcement report.

There are already some existing systems for us to find out from Europe when recalls are published, and so forth. They're not organized for the whole European Union,

and organized.

So, one of the things that we realized in putting together, particularly this aspect of the alert system, that a lot of this information is already known, but will now be organized, you know, in a more coherent fashion over the whole European Union.

So hopefully even today, if such a recall would exist, and it would have an effect on a licensing application, and so forth, that we would already be aware of that information, through some formal and informal means that already exist.

MS. HENRY: I just wanted to add one point. Sylvia Henry. The structure of the alert system itself is to make sure the information, as Joseph mentioned, the information that we have in the US is the same information that our EU member states counterparts have.

So when -- and when we are alerted

of a Recall Classification One, the EU has that same information. So, it's not a delayed process; everything is published.

MR. GAYLORD: We now have a legal question, it is as follows, but there is not a name or organizational affiliation.

It says, "Under what legal authority can the FDA make the Joint Sectoral Committee closed to the public"?

MR. FAMULARE: Closed?

MS. HORTON: Closed to the public.

MR. GAYLORD: Linda?

MS. HORTON: The Joint Sectoral Committee is a traditional bi-lateral government to government meeting. It is not in any way subject to one of the openness provisions of the statute. We have other ways of assuring public transparency. We're very committed to public transparency. That's why we're having this meeting.

But the Joint Sectoral Committee itself is a bilateral government to

government meeting.

MR. GAYLORD: Any other panelists like to address that? Raymond?

MR. MARS: I'm not sure where the question was directed. But it was, the meeting as an example we had here in May, I think, you know, we view that as a deliberative process meeting. So, you know, again we're trying to work to get things accomplished.

I think at that point, we probably have not invited the public, and I don't imagine we will in the future. We do make the outcomes of those meetings public. That's what happened with the press statement -- so there's an effort made to advise the public of what happens during those meetings. It is posted on the Web site, too. So it's available on the Internet.

MR. GAYLORD: All right. Would the individual that authored this particular

question, are they here? Would they like to identify themselves? Your name, please? Can you use the microphone, please?

MS. RODRIGUEZ: Yeah. My name is Rina Rodriguez. I work for Community Nutrition Institute. Just a quick comment, I guess. From what I'm hearing, it sounds like groups like -- and others really aren't going to know until the decisions have been made. It sounds like everything's closed, and then we'll find out afterwards.

I have a problem with that. Does anyone have a comment about that? We'd like to know. The decisions, you know, which countries are being reviewed? Not after the fact, as kind of -- have decided, but a little earlier in the process.

MR. GAYLORD: Joseph?

MR. FAMULARE: Just to bring up your concern there. It's important to remember that in assessing the equivalence of a particular authority, it is a deliberative

process. There will be a lot of very frank, back and forth discussion as to certain laws, regulations, the way inspections are conducted, and so forth, that will be done, but really not finalized at that time.

Things will happen to change, the way we think about something, when more information comes forward, and so forth. So, it wouldn't be fair, and it wouldn't chill. It would maybe chill the effect of our doing a very frank and detailed evaluation.

Just like, if I could draw a parallel, when we inspect a firm, we're not giving the public a blow by blow of every issue that comes up during an inspection. We wait until the end of the inspection, when things have been settled and then, under FOI, the report can be revealed. Then, there's been proper opportunity on both sides to ask and answer questions.

This is just an example of a parallel as to how we do an equivalent

assessment of a particular member state authority. We will come in, or the European Union will come here, and we'll ask very direct, frank questions. Look very intently at things. Certain conclusions may be derived very early on, which may not be accurate, once there's been an opportunity to answer them.

That's why our Freedom of Information laws allow for such discretion in releasing such information. Wait until all parties have been heard, for things to be released at the end of the process.

But we have endeavored and committed to make things as open and publicly transparent as possible, as we said in the rule making process, to publishing the final rule, in terms of having these meetings on an annual basis. In terms of posting what we can post on a Web site and having that open docket to receive information on anything that could affect our process.

MR. GAYLORD: Any other panelists like to address that? Our next question is from Mr. Rex Rhein, of Scrip World Pharmaceutical News. It's a two part question.

It says, "Only five countries showed up at the May meeting. Are these the ones FDA will look to first in the equivalence determination"? The second part is, "Who were the observers"? Raymond? Brian?

MR. HASSELBALCH: They, of course, selected who would attend. I don't know how they did it. But it -- certainly, some of the big ones there. The obvious ones, like UK, Germany, France. Italy I don't believe was represented there, of course, a very big manufacturer of pharmaceutical products, as well as active ingredients, was all there.

But there's no relationship between those who attended on behalf of the EU, and which member states will choose earlier than

later in the process.

MR. GAYLORD: Are there any additional questions that the audience has, that they would like to make at this time? Yes, please? Mr. Holmes?

MR. HOLMES: In the document that was published after the May meeting, there was a section in heavy type in the middle of the document which I was led to believe indicated that there were doubts being expressed during the meeting. That the commitment of the FDA to complete the review of all member states during the three year transition period.

I've been hearing this morning that there now does appear to be a commitment to complete the process within the three year period. I'd like to know if that could be confirmed. I'd also like to know if you have any start date for the joint inspections which will be undertaken, or the joint visits. Because we expected those to kick

off in September ’99. They still haven’t seen anything happen.

MR. FAMULARE: If I could speak to the discussion that was held at the May meeting. We expressed our plan, and how it would be laid out. We made it very clear, as we have had, even before that meeting, in other forms, that we will conduct the equivalency assessments in accordance with our available resources.

Does that mean that every authority will be brought to a finding of equivalence? It may or may not and we wanted to make that very clear to our European counterparts. They of course, expressed, as we’ve said here earlier, that well they felt either all authorities we found equivalent, or we extend the transition period.

We reiterated how we did not feel that the Agreement stated that. How there’s an Article which addresses resource, you know, limitations, and how we’ll make our

best faith effort. Are we committed to do our best faith effort to look at each member state over the next three years? Yes. We will commit to do our best faith effort.

That depends upon, again, the availability of resources within FDA, commitments from all centers and the field organizations which are represented here by high management. We hope that they'll be able to put forward those resources. But again, we have to realize the realities of FDA's main public health mission, to do its work, its inspections.

We have to realize that there are factors that weigh in in doing that process, as resource considerations. In terms of, for example, receiving documentation from all of the member states, as Sylvia broached on in her discussion, these things are now being received in the languages of the member states, and calls upon us to look at more resources to obtain translations. May cause

more delay in the process.

So that's a very important encumbrance that we're trying to overcome right now. In reviewing the paper submissions, as Brian mentioned, we're in the first phase of the process.

If you're looking for when the actual on site audits will begin, we actually didn't anticipate the on site audits to start until those paper processes were done. That will not be until we get into the phase which will obviously bring us into the next year.

Again, it depends on the flow of the -- on our ability to get the paper review completed.

MR. HASSELBALCH: Brian Hasselbalch. To clarify, the September '99 date that you're referring to as to the start date of the inspection audits, is actually a planning date for us to begin the process of preparing for those inspection audits. We never intended they would start September

of ’99.

Nonetheless, we are delayed a little bit in our projection, at least, in meeting our projection as to when we would start. I’ve learned enough now to know not to give you a month. But perhaps sometime mid-year 2000 we might be in a position to begin inspection audits. Which means by then we’ll have to have reviewed at least one member state’s documentation. We’ll have had to have completed at least one member state’s system audit.

MR. FAMULARE: With the idea, Joe Famulare again, with the idea that we had sufficient basis to do the on site audit in the paper review that we did. We found sufficient and adequate laws, directives, and so forth.

Because obviously if on the paper review we hadn’t even broached that, that threshold, we would want to correspond and discuss those problems before we invested the

resource into the on site audit.

MR. GAYLORD: Are there any additional questions that anyone would like to ask at this time? Certainly we've had a nice cross section of questions, and we appreciate that very much.

ADJOURNMENT

When we convened the panels, there were two representatives that I neglected to mention, that I'd like to mention now. One is a member of the Project Management Team, and that's Ms. Judith Gushee. She's from the Center for Veterinary Medicine. Also, Dr. Robert Livingston is also from that Center, as well.

So, each of those Centers, the Center for Drugs, Biologics, as well as Veterinary Medicine, working with the Office of Regulatory Affairs, and the General Counsel's Office, working in concert, in terms of implementation at this particular time.

In addition, both Walter Batts and Linda Horton were involved in negotiation processes of the MRA, Walter on the pharmaceutical GMP side, and Linda on the medical devices side. So there's been a continuum in this Agreement that will continue as time goes on, to bear fruit.

So, this morning we've looked at a number of the people that have been involved in helping to negotiate and implement this Mutual Recognition Agreement for Pharmaceutical Good Manufacturing Practices.

As the Agency and the EU work together to fulfill the Agreement in its entirety, there are three keys that the Agency would like you to remember. First, a thorough assessment is going to take place. Secondly, the process will take time, as it is resource intensive. Third, a determination about equivalence for each of the member states will occur.

I want to thank each one of you for

being here, and joining us today, and participating in today's meeting. As Sharon Holston mentioned, this is a third in a series of public meetings that will continue to be held, so that our constituents are informed about this process.

But it's more than about informing. It's also, as Sharon mentioned, a dialogue that we engage in. So, it's necessary to have feedback from all of our constituents: industry, consumers, and so forth. Health advocates, whatever the communities that FDA serves, we need your input as we proceed.

So therefore, as was mentioned a couple times this morning, we have the open docket, which is 98S- 1064. We welcome and ask that you would submit your comments that you have. I noticed when I talked to some people on the phone, they stated that they would submit detailed comments for the record. That is much appreciated.

If you need the address to send

that to, please see me, or any of the other Agency officials that are present today. I'd like to thank each of the presenters and the panelists for coming here today. They wanted to share their expertise with you firsthand and the offices that worked with the Office of International Programs in putting the meeting on.

The Office of Consumer Affairs, we've worked with Chandra Smith Collier there. We've worked with the Office of Legislative Affairs, Michael Eck was there. Ken Nolan, in the Office of Public Affairs, who was very helpful in contacting industry groups. Barbara Steller in the Center for Devices and Radiological Health. Each of them played a role so that we'd have as many people here as possible.

Last but not least, in helping to put the meeting, in their thousand and one details have to be attended to, Erik Henrikson worked tirelessly to help this

meeting be possible. So he's in the back, Erik. That is appreciated.

Finally, the hard work of the Project Management Team, and Agency officials, as well as their counterparts in the EU is much evident I think from the information that's been presented. As they continue to work together, they will strive to bring the promise of this Agreement to fruition. There are some uncertainties. But the commitment on both sides is to implement this Agreement as quickly and as expeditiously as possible for the good of the public health.

So, thank you for attending. For the hand-outs that are here, please help yourselves to them. If there's any follow-up information, please see us, that we can help you with. Thank you.

(Whereupon, at 12:00 p. m. , the PROCEEDINGS were adjourned.)

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